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TITLE: Validating Diagnostic and Screening Procedures for Pre-Motor Parkinson's Disease

PRINCIPAL INVESTIGATOR: Dr. J William Langston

CONTRACTING ORGANIZATION: Parkinson's Institute

Sunnyvale, CA 94085-2934

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## **INTRODUCTION**

This work addresses the next frontier in Parkinson's disease (PD) research: developing new tools to diagnose PD in its earliest stages, well before motor symptoms manifest. Currently, PD is diagnosed only when classic motor features present, when 60-80% of striatal dopamine is already depleted. Clinical trials with neuroprotective agents are much more likely to succeed if carried out before the major portion of the damage has already been incurred. However, these transformative goals will be clinically useful for screening the general population only if non-invasive tools can be easily administered in the primary care physician's office. Our hypothesis is that cardiac autonomic dysfunction assessed as heart rate variability (HRV) using a standard EKG, in combination with hyposmia and other simple screening tests, will be highly predictive of abnormalities in dopamine transporter (DAT) imaging and ultimately predict the emergence of full-blown PD or a related Lewy body disorder. The ability to identify individuals with pre-motor PD could have enormous public health consequences, particularly once an effective disease-modifying therapy is identified. Our goal is to develop a battery of tools to identify pre-motor PD that can be administered with relative ease and low cost, such that it can be incorporated into a routine annual physical examination, beginning when individuals reach an age where they are at increased risk for PD.

## **BODY**

This 24-month proposal will establish the critical infrastructure for the initiation of a five year prospective follow-up study to identify those at risk for developing PD or a related Lewy body disorder in three study populations. The current proposal has four objectives: 1) to develop the required internal and collaborative infrastructure to establish a large cohort with idiopathic REM behavior disorder and test a comprehensive clinical assessment protocol for pre-motor PD, 2) to establish a protocol for collecting digital EKGs from collaborating studies, 3) to initiate data collection in each study population, and 4) to conduct preliminary analyses of EKG data for HRV. On January 28, 2013 we requested a 12-month extension of the Period of Performance to support completion of the above award. The extension was approved on January 31, 2013 (revised period of performance April 30, 2014, research ending March 31, 2014). On March 14, 2014 we requested a second 12-month extension of the Period of Performance to support the completion of the above award. Regulatory approval of the project was extremely complicated, requiring review and coordination between the regulatory agency of the Parkinson's Institute and the USAMRMC HRPO. The approval delays prevented initiation of the actual human contact work and receipt of data from collaborating institutions for a prolonged time. After HRPO approval was received, enrollment of eligible subjects has proceeded more slowly than anticipated. However, we have made major progress toward completion of the statement of work and have developed effective case recruitment methods. Substantial progress has been made utilizing these new recruitment methods. The newly approved extension is effective April 1, 2014 (revised period of performance is April 30, 2015, research ending March 31, 2015). With approval of the extension, we expect to accomplish the funded work as originally described. There have been no modifications to the statement of work as originally

awarded.

## **KEY RESEARCH ACCOMPLISHMENTS AS OF 31 MARCH, 2014**

### **1) Assemble an iRBD Cohort:**

- a) Identify eligible iRBD patients and controls
  - i) Establish collaborative relationships with all San Francisco Bay Area sleep medicine clinics
  - ii) Develop physician outreach methods and materials
  - iii) Develop community outreach methods and materials
  - iv) Develop RBD screening methods to identify likely cases

#### ***Progress to date:***

- *Cohort recruitment is ongoing*
- *We have, and continue to actively establish collaborative relationships with San Francisco Bay Area sleep medicine clinics*
- *Physician outreach materials have been developed. Materials continue to be distributed to sleep clinics and neurologists in the region*
- *Subject recruitment materials have been developed and IRB approved, and continue to be distributed*
- *Direct outreach recruitment methods are being implemented*

#### ***Milestones Remaining:***

- *Complete iRBD case and control recruitment (estimated completion: December 31, 2014)*

- b) Standardize application of diagnostic criteria for iRBD.
  - i) Develop methods for rescoring polysomnographic (PSG) data and applying diagnostic criteria

***Progress to date:*** *Completed. As specified in the study protocol, some subjects with suspected iRBD have undergone de novo PSGs. De novo PSGs will continue to be conducted as needed.*

- c) Develop a secure database to track subject recruitment and enrollment efforts

***Progress to date:*** *Completed. A secure relational database has been developed and continues to be populated.*

- d) Prepare and submit study documents for institutional review board (IRB) approval
- Progress to date:*** *Completed. Continuing review documents were submitted to El Camino Hospital on October 29, 2013. These were reviewed and approved by the El Camino Hospital IRB at their meeting on November 15, 2013 and we received the new approval letter from the El Camino Hospital IRB on November 19, 2013. The study expiration date is November 15, 2014. There were no modifications to the protocol or consent forms since these documents were last submitted to HRPO. On January 9, 2014 we sent the continuing review report, new approval letter from the El Camino IRB, current protocol and current consent forms to Ms. Kirdnual at USAMRC ORP HRPO.*

- e) Develop the clinical assessment protocol
  - i) Develop standardized clinical data collection protocols
  - ii) Create scannable data collection forms for all clinical instruments
  - iii) Develop blood processing and storage protocols
  - iv) Pilot test clinical data-collection methods

***Progress to date:*** Completed

- f) Develop an operations manual

***Progress to date:*** Completed

- g) Develop clinical databases, a data dictionary and quality assurance procedures

***Progress to date:*** Completed

- 2) Establish digital EKG collection in the APDC cohort: We will work with APDC staff to establish a protocol for collection of digital EKGs and transfer of data to the Parkinson's Institute

***Progress to date:*** Completed

- 3) Establish a study steering committee:

Convene a steering committee meeting at the Parkinson's Institute

***Progress to date:*** Estimated completion: December 31, 2014

- 4) Implement data collection in each study population:

- a) iRBD cohort: Begin enrolling and characterizing iRBD subjects
- b) PARS cohort & APDC cohorts: Baseline digital EKG data will be collected at regular follow-up assessments and transferred to the Parkinson's Institute at regular intervals using secure protocols

***Progress to date:*** USAMRC ORP HRPO approval has been received to establish an iRBD cohort, and to receive de-identified data from PARS and APDC.

- iRBD cohort enrollment has commenced. Clinical evaluations and DaTSCAN imaging are ongoing. Estimated completion: December 31, 2014
- PARS EKG data transfers have commenced and are ongoing. Estimated completion: September 30, 2014
- APDC EKG data transfers have commenced and are ongoing. Estimated completion: September 30, 2014

- 5) Data analysis:

- a) Digital EKG data will be analyzed for 15 HRV parameters
- b) Descriptive analyses for each cohort, and preliminary explorations of associations between HRV, hyposmia and other putative pre-motor features will be performed as possible, based on subject accrual

***Progress to date:***

- HRV analyses of EKGs obtained from PARS are ongoing. Estimated completion: December 31, 2014
- HRV analyses for EKGs obtained from APDC are ongoing. Estimated completion: December 31, 2014

- *HRV analyses for EKGs obtained from the iRBD cohort are ongoing. Estimated completion: January 31, 2014*
- *Descriptive analyses and preliminary explorations of associations are pending completion of data collection. Estimated completion: March 31, 2015*

## **REPORTABLE OUTCOMES**

None at this time.

## **CONCLUSIONS**

Substantial progress has been made. Important next steps for the project include the following:

- *continue to ascertain, enroll and clinically evaluate iRBD cohort members*
- *ongoing receipt and analysis of de-identified data from PARS*
- *ongoing receipt and analysis of de-identified data from APDC*
- *convene a study steering committee meeting*
- *ongoing data entry and quality assurance processes*
- *develop and implement an analytic plan*

## **REFERENCES**

None

## **APPENDICES**

None